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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,877	06/21/2006	Jonathan Henry Ellis	PB60608	8672

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EXAMINER	
MACFARLANE, STACEY NEE	
ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
03/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/583,877	ELLIS ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22 and 24-33* is/are pending in the application.

4a) Of the above claim(s) *4,6,7,9,10,14,15,17,18,20,22 and 24-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 8, 11-13, 16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-20, 22, and 24-33 are pending in the instant application. Applicant's election of Group I and the species of the species of antibodies that bind to residues 586-685, the combination of heavy chain SEQ ID NO:37 in combination with light chain SEQ ID NO:40, and a combination of CDRs 1-6, in the reply filed on December 10, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicant failed to provide a listing of claims that read upon the elected invention. Claims 4, 6-7, 9-10, 14-15, 17-18, 20, 22, and 24-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 10, 2007.

3. Claims 1-3, 5, 8, 11-13, 16 and 19, in so far as they read upon the elected invention, will be considered upon their merits in the instant office action.

Sequence compliance

4. Claims 5 and 13 are not in compliance with the requirements for Sequence Identifiers (see MPEP 2422.03). The appropriate format for sequence identifiers is SEQ ID NO: X, wherein "X" is the sequence number. Appropriate correction is required.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3, 5, 8, 13, 16 and 19 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims do not sufficiently distinguish over antibodies that exist in nature. Antibodies that bind to and neutralize human NOGO are naturally occurring products and are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980) and MPEP 2105. Claims should be amended to indicate the hand of the inventor, for example by insertion of "Isolated" as taught by paragraphs 0023 and 0162 and of the instant specification.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 5, 8, 11-13, 16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Regarding claim 1, the phrase "e.g." renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

9. Claim 1 is vague and indefinite in so far as it employs the term "NOGO" as a limitation. It is unclear what protein or isoform the claims encompass, and without a reference to a precise amino acid sequence identified by a proper SEQ ID NO: one cannot determine the metes and bounds of "NOGO". Moreover, because the instant specification does not identify that property or combination of properties which is unique to and, therefore, definitive of human "NOGO", an artisan cannot determine if a compound which meets all of the other limitations of a claim would then be included or excluded from the claimed subject matter by the presence of this limitation.

10. Claims 2 and 3 are vague and indefinite for their reference to a particular portion of an amino acid structure without proper disclosure of the whole structure itself (See section 8 above).

11. Claim 8 is vague and indefinite in its recitation of CDRH1, CDRH2, and CDRH3 in parent claim 5. Claim 5 recites heavy chain CDRs: 4, 5 and 6, not 1, 2, and 3. In the interest of compact prosecution Examiner has interpreted these as a numerical error.

12. Claims 5, 11-13, 16 and 19 are indefinite for depending from indefinite claims.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to an antibody comprising heavy and light chain variable regions that comprising one or more CDRs selected from CDRL1, CDRL2 and CDRL3. The claims read on an antibody with alterations in the CDRs.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. MacCallum et al. J. Mol. Biol. (1996) 262, 732-745, analyzed many different antibodies for interactions with

antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left column). Pascalis et al. The Journal of Immunology (2002) 169, 3076-3084 demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (2003) BBRC 307, 198-205, which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). Vajdos et al. (2002) 320, 415-428, additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.). Holm

et al. (2007) 44, 1075-1084 describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen et al. J. Mol. Bio. (1999) 293, 865-881. describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu et al. J. Mol. Biol. (1999) 294, 151-162. state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation. The references demonstrate that an antibody must comprise all 6 CDRs (each of the CDRs: CDRH4, CDRH5 and CDRH6 and each of the light chain variable domains of CDRL1, CDRL2 and CDRL3 in order to maintain the antigen binding specificity and affinity which is characteristic of the immunoglobulin.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-3, 11 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Caroni et al., Neuron, 1(1):85-96, published 1988, as evidenced by Zander et al. Journal of Molecular Recognition, 20:185-196, published May 2007.

17. Claims are drawn to an antibody or functional fragment thereof which binds with and neutralizes human NOGO; binding a region of human NOGO-A protein between amino acids 586-785; the elected species of amino acids 586 to 685; wherein the antibody is monoclonal; and pharmaceutical compositions comprising an anti-NOGO antibody with a pharmaceutically acceptable diluent or carrier.

18. The Caroni reference teaches a monoclonal antibody, named IN-1, raised against proteins that demonstrate non-permissive substrate properties for neurite growth and fibroblast spreading, which had been extracted from rat CNS myelin fractions. The monoclonal antibody IN-1 is demonstrated as neutralizing this neurite inhibition upon injection of a pharmaceutical composition comprising IN-1, leading to aberrant growth of optic nerve axons.

The secondary Zander reference is relied upon to demonstrate the inherent ability of the IN-1 antibody to bind to human NOGO-A protein between amino acids 586 and 685. Section 2131.01 of the MPEP discusses the proper application of a secondary reference as supportive evidence in a rejection under 102(b) stating, “To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary

skill." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). While section 2124 of the MPEP explains the proper use of references that are not available as prior art stating, "In certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. *In re Wilson*, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism". Although the Caroni reference teaches an antibody that is identical to that of instant claim 1, the substrate and the precise epitopes to which the monoclonal IN-1 antibody binds were not known at the time of the Caroni publication. It was only later that IN-1 was found to specifically bind NOGO-A or Reticulon-4, and it was only through the epitope mapping of IN-1, as taught by the Zander reference (Figure 2), that it was demonstrated that a "strong conformational dependence" was necessary for antibody-antigen binding (page 194, paragraphs 1-2) of IN-1 to human NOGO-A. In other words, the rather weak but highly specific antibody-antigen interaction between IN-1 and human NOGO-A could not be mapped to a linear epitope, but rather involves binding to the protein as a whole, including residues 586-685 of the instant claim 3. Thus, the Caroni reference teaches the neutralizing antibody of the instant claims and case law clearly states that something which is old does not become patentable upon the discovery of a new property.

> "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old

composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Thus, the claiming of a new use, new function or unknown property that is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Further, *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." In addition the court has held that there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); *Abbott Labs v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999).

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established and the burden of proof rests upon the Applicant to demonstrate that the

prior art does not necessarily or inherently possess the characteristics of Applicant's claimed product. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

19. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Fiedler et al. Protein Engineering 15(11):931-941, published November 2002.

20. Claim 12 is drawn to a humanized or chimeric antibody which binds to and neutralizes human NOGO.

21. The Fiedler reference teaches a neutralizing chimeric and partially humanized IN-1 antibody (antibody II.1.8 of the reference, see page 932, column 2, paragraph 2 for construction details) designed to improve the low antigen affinity of IN-1 to human NOGO-A . The engineered antibody of the Fiedler reference demonstrates enhanced neutralizing activity (abstract).

22. The Zander et al. reference is relied upon to demonstrate that the ability of this engineered IN-1 antibody to bind human NOGO-A, including a region between amino acids 586-685, was an inherent feature of the prior art antibody (page 190, paragraph 2 and page 192, paragraph 2). Thus, the antibody of the Fiedler reference fully anticipates the antibody of instant claim 12.

Allowable Subject Matter

23. Claims 5, 13 and 16 are objected to as being dependent upon a rejected base claim, but appear to be free of prior art and would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

24. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M,W and ALT. F 6 am to 3 pm, T & R 5:30 am - 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
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